APPENDIX A
ROBUST SUMMARY FOR m-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
m-Ethylphenol (CAS 620-17-7)

Type	: Melting Point
Value	: -4.0 ^{o}C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: 1955 or earlier
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Terres, *Brennstoff Chemie*,36,272 (1955)

Type	: Boiling Point
Value	: 218.42 ^{o}C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type	: Vapor Pressure
Value	: 0.05 mmHg at 25^{o}C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Estimated < 5% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR values regressed from seven literature references.

Type : Partition Coefficient
Value : Log Kow = 2.77
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Water Solubility
Value : 2.3 wt % at 127.3 ^{o}C
Method : Unknown
GLP : Unknown
Year : 1955 or earlier
Remarks : Expected to be slightly soluble @ 25^{o}C
Quality : Unknown
Reliability : (2) Reliable with restrictions

(5) Terres, *Brennstoff Chemie*, 36, 272 (1955)

Type : pKa Value
Value : 10.17 @ 20^{o}C
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(6) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ENVIRONMENTAL FATE ELEMENTS
m-Ethylphenol (CAS 620-17-7)

Type : Atmospheric fate
Value : T1/2 = 5 hours
Method : Structure activated method
GLP : Unknown
Year : 1993
Remarks : Vapor-phase m-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 8.4x10S-11 cc/molecule-sec @ 25^{o}C
Quality : Unknown

Reliability : (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Aqueous aerobic degradation
Value : 93% removal in 37 days
Method : Water column passed through acclimated soil
GLP : Unknown
Year : 1989
Remarks : Laboratory study
Quality : Unknown
Reliability : (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX B
ROBUST SUMMARY FOR o-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
o-Ethylphenol (CAS 90-00-6)

Type : Melting Point
Value : -3.3 ^{o}C
Decomposition : No
Sublimation : No
Method : Unknown
Year : 1963 or earlier
GLP : Unknown
Remarks : None
Quality : Estimated < 1% error
Reliability : (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR value taken from Biddescombe, *J. Chem. Soc.*,5764, (1963)

Type : Boiling Point
Value : 204.5 ^{o}C
Decomposition : No
Sublimation : No
Method : Unknown
Year : Unknown
GLP : Unknown
Remarks : None
Quality : Estimated < 1% error

Reliability : (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type : Vapor Pressure
Value : 0.16 mmHg at 25^{o}C
Method : Calculated from vapor pressure constants in reference
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Estimated < 5% error
Reliability : (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR values regressed from nine literature references.

Type : Partition Coefficient
Value : Log Kow = 2.72
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Water Solubility
Value : 5340 mg/L @ 25^{o}C
Method : Uknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(5) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : pKa Value
Value : 10.47 @ 20^{o}C
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(6) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ENVIRONMENTAL FATE ELEMENTS
o-Ethylphenol (CAS 90-00-6)

Type	: Atmospheric fate
Value	: T1/2 = 9 hours
Method	: Structure estimated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase o-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 4.2 x 10E-11 cc/molecule-sec @ 25^{o}C
Quality	: Unknown
Reliability	: (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous anaerobic degradation
Value	: 23-42% removal in 8 weeks
Method	: Groundwater column inoculated into anaerobic digestor
GLP	: Unknown
Year	: 1983
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX C
ROBUST SUMMARY FOR p-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Melting Point
Value	: 45.08^{o}C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown

GLP : Unknown
Remarks : None
Quality : Estimated < 5% error
Reliability : (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type : Boiling Point
Value : 217.99 ^{o}C
Decomposition : No
Sublimation : No
Method : Unknown
Year : Unknown
GLP : Unknown
Remarks : None
Quality : Estimated < 1% error
Reliability : (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type : Vapor Pressure
Value : 0.07 mmHg at 25^{o}C
Method : Calculated from vapor pressure constants in reference
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Estimated < 10% error
Reliability : (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR values regressed from three literature references.

TYPE : Partition Coefficient
Value : Log Kow = 2.68
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Log Kow
Value	: 2.66 / 2.81
Method	: Unknown / Calculated
GLP	: Unknown / Unknown
Year	: Unknown / Unknown
Remarks	: None / None
Quality	: Unknown / Unknown
Reliability	: (2) Reliable with restrictions

(5) Verschueren, "Handbook of Environmental Data on Organic Chemicals"

Type	: Water Solubility
Value	: 4900 mg/L @ 25^{o}C
Method	: Uknown
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(6) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.38 @ 20^{o}C
Method	: Unknown
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(7) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ECOTOXICITY ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Acute
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Flow-through
Exposure period	: 96 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: 0, 10.5, 16.1, 24.8, 38.2 and 58.9 mg/l, analytical verification
Control group	: Untreated
LC50	: 10.4 mg/l

Method	: Evaluate test water quality, fish behavior and pharmacotoxic signs, body weight and survival.
Year	: 1985
GLP	: Not stated
Test substance	: 4-ethylphenol 99% pure
Reliability	: (2) Reliable with restrictions

(8) Geiger, D. L., et al., Acute toxicities of organic chemicals to fathead minnows, Vol. III. Center for Lake Superior Environmental Studies, U. of Wisciensin – Superior. US EPA Cooperative Agreements Superior, WI., p 195, 1985.

ENVIRONMENTAL FATE ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Atmospheric fate
Value	: T1/2 = 9 hours
Method	: Structure estimated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase p-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 4.2 x 10E-11 cc/molecule-sec @ 25^{o}C
Quality	: Unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: 76% removal in 37 days
Method	: Water column passed through acclimated soil
GLP	: Unknown
Year	: 1989
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX D
ROBUST SUMMARY FOR m-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeated dose
Species	:	Rat
Sex	:	Male
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	28 d
Frequency of treatm.	:	Daily
Post exposure period	:	No
Doses	:	0, 20, 150, 500 mg/kg diet (approx. 0, 1.86, 13.95 or 45.8 mg/kg bw/d)
Control group	:	yes, concurrent no treatment
NOAEL	:	ca. 45.8 mg/kg bw
Method	:	other: 10 rats/group, TS was prepared as a 2.0% corn oil solution and blended with the diet; diets were prepared fresh weekly. Control rats received basal diets containing 2% corn oil, necropsy of all animals
Year	:	1969
GLP	:	no data
Test substance	:	other TS: M.P.:11-12 C; B.P.: 202.8 C
Result	:	No deaths occurred during the study and no untoward behavioural reactions were noted. At necropsy, no significant gross lesions were noted among the test animals, when compared to the control animals.

(1)

Type	:	Repeated dose
Species	:	Rat
Sex	:	male/female
Strain	:	other: F344/N
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	continuously in diet
Post exposure period	:	No
Doses	:	0, 300, 1000, 3000, 10000 or 30000 ppm (see remarks)
Control group	:	Yes
NOAEL	:	10000 ppm
Method	:	other: 5 rats/sex and dose, clinical observations twice daily, body weight initially, weekly and at termination, gross and microscopic examination, statistical analysis
Year	:	1991
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25

		300 ppm 25 25 1000 ppm 85 82 3000 ppm 252 252 10000 ppm 870 862 30000 ppm 2470 2310
Result	:	no mortallity; no clinical signs of toxicity were observed and no gross lesions were noted at necropsy >= 10000 ppm: increased relative liver weights for males and females, but no histomorphologic changes 30000 ppm: decreased mean final body weights and mean body weight gains for males and females; reduced food consumption in males and females during the first week of the study; relative kidney weight marginally increased in males and females but no histomorphologic changes; minimal to mild uterine atrophy in 4 of 5 females NOAEL: male: 870 mg/kg bw NOAEL: female: 862 mg/kg bw
Reliability	:	(1) valid without restriction

(2)

Type	:	Repeated dose
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	13 w
Frequency of treatm.	:	once daily
Post exposure period	:	1 w
Doses	:	0, 50, 150 or 450 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
Method	:	other: 30 rats/sex/dose, add.10 rats/sex for baseline clin. Pathol., interim kill at week 7, terminal kill at week 14, blood samples for hematology, clin.chemistry; urinalysis; gross and microsc. pathology; stat. anal.: Dunnett's t-t
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: purity: 98.6%
Result	:	signs of intoxication: 450 mg/kg bw, male, female: lethargy, tremors, hunched posture, dyspnea; >= 150 mg/kg bw: slight reduction in body weight gain of males 450 mg/kg: one high dose male was found dead on day 5 (cause not evident), reductions in weight gain for males and females; treatment-related gross and histomorphologic lesions not evident NOAEL: 50 mg/kg bw (male) NOAEL: 150 mg/kg (female)
Reliability	:	(2) valid with restrictions

(3)

Type	:	Repeated dose
Species	:	Rat
Sex	:	male/female
Strain	:	other: CD
Route of admin.	:	Gavage
Exposure period	:	13 w
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	50, 150 or 450 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
LOAEL	:	ca. 50 mg/kg bw
Method	:	other: 10 rats/sex and group, observation of clinical signs, performance of neuro-behavioural test batteries, gross pathologic and histopathologic evaluation
Year	:	1986
GLP	:	no data
Test substance	:	other TS: no data on purity
Result	:	>= 50 mg/kg: salivation, hypoactivity, rapid laboured breathing 450 mg/kg: one female was found dead; increased closing of eyelids, pollakisuria (females), reduced food consumption; few significant changes in the performance of the neuro-behavioural test batteries (no further details reported); no brain weight changes, no gross or histopathological lesions in the brain or other nervous tissue

(4)

Type	:	Repeated dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	continuously in diet
Post exposure period	:	No
Doses	:	0, 300, 1000, 3000, 10000 or 30000 ppm (see remarks)
Control group	:	Yes
NOAEL	:	ca. 3000 ppm
Method	:	other: 5 mice/sex and dose, clinical observations twice daily, body weight initially, weekly and at termination, organ weights recorded and microscopically examined, statistical analysis
Year	:	1991
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	53	66
1000 ppm	193	210
3000 ppm	521	651
10000 ppm	1730	2080
30000 ppm	4710	4940

Result	:	mortality: 0 ppm: 1/5 male; 10000 ppm: 1/5 females; 300000 ppm: 2/5 males, 2/5 females;

males, 2/5 females;
Signs of toxicty: male, female; >= 100000 ppm:
hunched posture, rough hair coat, laboured respiration (only females), additionally at 30000 ppm: thin appearance, lethargy and tremor
relative liver weight increased: male from 3000 ppm, female from 300 ppm
relative kidney weight increased: male at 3000 ppm, female at 30000 ppm
histomorphology: female: 30000 ppm: mammary gland, ovarian and uterine atrophy

NOAEL (male): 521 mg/kg bw
NOAEL (female): 651 mg/kg bw

Reliability : (1) valid without restriction

(2)

Type	:	Repeated dose
Species	:	Mouse
Sex	:	Female
Strain	:	other: CBA/J
Route of admin.	:	Dermal
Exposure period	:	6 w
Frequency of treatm.	:	3 times/week
Post exposure period	:	6 months
Doses	:	0.5 % in acetone
Control group	:	Yes
Method	:	other: 5 rats, application of the substance to depilated or clipped lower back by mist spray; observation of the hair colour of the new hair regrowth were made weekly
Year	:	1974
GLP	:	no data
Test substance	:	other TS: no data on purity

Result : No depigmentations of the regrowthed hair were observed.

(5)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Sister chromatid exchange assay
System of testing	:	human lymphocytes
Test concentration	:	0 -1.0 Mm
Metabolic activation	:	no data
Result	:	Negative
Method	:	other: solvent: DMSO:EtOH (1:1), culture time 88-90 h
Year	:	1986
GLP	:	no data
Test substance	:	other TS: purity: 99.2%

(6)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538

Test concentration	**:**	over a wide dose range (no further information) in DMSO
.		
Metabolic activation	**:**	with and without
Result	**:**	Negative
Method	**:**	other: according to Ames, Proc.Natl.Acad.Sci.70, 2281(1973); Mutat.Res.31,347(1975); Nestmann, Cancer Res.39.4412(1979); Environ.Mutagen.1,361(1979)
Year	**:**	1980
GLP	**:**	no data
Test substance	**:**	other TS: purity no data
Remark	**:**	presumbly negative, but solubility did not allow the testing of the compound in amounts that result in bacterial toxicity

(7)

Type	**:**	Ames test
System of testing	**:**	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	**:**	no data
Metabolic activation	**:**	with and without
Result	**:**	Negative
Method	**:**	other: according to Ames, Mutation Res. 31, 347 (1975)
Year	**:**	1980
GLP	**:**	no data
Test substance	**:**	other TS: no data on purity

(8)

Type	**:**	Unscheduled DNA synthesis
System of testing	**:**	rat hepatocytes
Test concentration	**:**	502, 251, 100, 50.2, 25.1, 10.0, 5.02, 2.51, 1.0, 0.502 ug/ml in DMSO
Metabolic activation	**:**	With
Result	**:**	Negative
Method	**:**	other: according to Williams, Cancer Res. 37, 1845 (1977); Williams cited in deSerres (eds): Chemical Mutagens, Vol 8, pp.61, 1980, Plenum Press, NY
Year	**:**	1988
GLP	**:**	Yes
Test substance	**:**	other TS: 99.8%
Remark	**:**	concentration range: 502 - 25.1 ug/ml: excessive toxicity
Reliability	**:**	(2) valid with restrictions

(9)

Type	**:**	Sister chromatid exchange assay
System of testing	**:**	human fibroblasts
Test concentration	**:**	0, 0.08, 0.8, 4 mM dissolved in ethanol; 8, 10, 30 mM dissolved in Eagle's Minimal Essential Medium (MEM)
Metabolic activation	**:**	Without
Result	**:**	Negative
Method	**:**	other: after add. of m-cresol incub. for 2h, then washing and add. of medium containing 15% fetal calf serum and BrdU for 48 h
Year	**:**	1984

GLP	:	no data
Test substance	:	other TS: purity: 99%
Remark	:	> 8 mM cytotoxic response
Reliability	:	(2) valid with restrictions

(10)

Type	:	other: DNA amplification
System of testing	:	SV40-transformed CHO cell
Test concentration	:	5.0 mM in DMSO
Metabolic activation	:	Without
Result	:	Negative
Method	:	other: cells were incub. for 4d with m-cresol, then viability of the cells was determined, SV40-DNA content was detected by hybridization according to Lavi, Proc.Natl.Acad.Sci. (USA) 80,6144,1981; Winocour, Proc.Natl.Acad. Sci. (USA)77,48
Year	:	1989
GLP	:	no data
Test substance	:	other TS: purity: 98%

(11)

Type	:	other: SV40 Mammilian Inductest
System of testing	:	Syrian hamster kidney cells (SV40)
Test concentration	:	0.0001-0.0000001 ml
Metabolic activation	:	Without
Result	:	Positive
Method	:	Other
Year	:	1983
GLP	:	No
Test substance	:	no data
Remark	:	Mammalian inductest

(12)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 100, TA 1530, TA 1535, TA 1538,TA 1950, TA 1951, TA 1952, G 46
Test concentration	:	0.5% in ethanol
Metabolic activation	:	no data
Result	:	Ambiguous
Method	:	other: according to Ames Mutat. Res. 31,347 (1975); Science 176, 47 (1972)
Year	:	1975
GLP	:	no data
Test substance	:	other TS: no data on purity
Remark	:	a questionable effect was produced in the strain TA 1535

(13)

Type	:	other: SOS-Chromotest

System of testing : Escherichia coli PQ37
Test concentration : no data

Metabolic activation : Without
Result : Positive
Method : other: After termination of the nitrosation of m-cresol with ammonium sulphamate, test was performed according to Quillardet, Mutat. Res. 147,65 (1985)
Year : 1989
GLP : no data
Test substance : other TS: no data

(14)

Type : other: Prophage induction assay
System of testing : Escherichia coli / Bacteriophage lambda

Result : Positive

Remark : abstract only

(15)

Type : Cytogenetic assay
System of testing : Allium cepa

Metabolic activation : Without
Result : Negative

Year : 1948
GLP : No
Test substance : other TS: no data on purity

Remark : marginal effects

(16)

Type : Mouse lymphoma assay
System of testing : L 5178 Y (TK +/-) cells
Test concentration : 13.0 - 520 ug/ml in DMSO

Metabolic activation : with and without
Result : Negative
Method : other: preliminary cytotoxicity tests, procedure according to Clive, Mutation Res. 31,17,1975; Clive, Mutation Res. 59,61,1979, colony size not reported
Year : 1988
GLP : Yes
Test substance : other TS: 99.8%

Reliability : (2) valid with restrictions

(17)

Type	:	Cytogenetic assay
System of testing	:	Allium cepa
Test concentration	:	0, 0.015, 0.02 and 0.025% in destilled water
Metabolic activation	:	no data
Result	:	Positive
Method	:	other: treatment period: 0: 3 hrs; 0.015 24 hrs; 0.02: 5 hrs; 0.025: 5 hrs
Year	:	1965
GLP	:	No
Test substance	:	other TS: no data on purity

(18)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration	:	0, 0.5, 5, 50,500, 5000 ug/plate dissolved in DMSO, highest dose toxic
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: plate incorporation assay according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1982
GLP	:	no data
Test substance	:	other TS: purity: 98%
Reliability	:	(1) valid without restriction

(19)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA 100, TA 1535, TA 1537
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31,347 (1975) and Yahagi, Cancer Lett. 1,91 (1975)<; to select dose range the chemical was checked for toxicity to S. typh. TA 100
Year	:	1983
GLP	:	no data
Test substance	:	other TS: 97%
Reliability	:	(1) valid without restriction

(20)

Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster Ovary (CHO) cells
Test concentration	:	0, 198,297,398,495 ug/ml DMSO without; 0, 250, 500, 699, 749, 799, 898, 998, 999, 1100 ug/ml DMSO with S9-mix (>=898 ug/ml: toxic)
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preliminary range finding studies; in accordance with OECD Guideline 473

Year	:	1988
GLP	:	Yes
Test substance	:	other TS: purity: 99.8%
Reliability	:	(1) valid without restriction

(21)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic assay
Species	:	other: mouse bone marrow cells
Sex	:	male/female
Strain	:	ICR
Route of admin.	:	Gavage
Exposure period	:	Once
Doses	:	0, 96, 320, 960 mg/kg bw in corn oil
Result	:	Negative
Method	:	other: in accordance with OECD Guideline 475, 5 mice/sex/dose, bone marrow cells, sacrifice 6, 24, 48 hrs post treatment
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 99.8%
Remark	:	dose finding study: see chapter 5.1
Reliability	:	(1) valid without restriction

(22)

Type	:	Sister chromatid exchange assay
Species	:	Mouse
Sex	:	Male
Strain	:	DBA
Route of admin.	:	i.p.
Exposure period	:	single application
Doses	:	0, 200 mg/kg bw dissolved in sunflower oil
Result	:	Negative
Method	:	other: 3/4 mice were partly hepatectomized 5 d prior to exposure, 0.5h later BrdU tablets were implanted s.c.; 17h later single i.p. inj. of colchicine, 4h later sacrifice: bone marrow cells, alv. macrophages, regen. liver cells
Year	:	1984
GLP	:	no data
Test substance	:	other TS: purity. 99%
Result	:	No increase in SCE frequencies in the intact mice as well as in the partially hepatectomized mice.

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage

Exposure period	:	day 6 through day 15 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	until gd 21
Doses	:	0, 30, 175 or 450 mg/kg bw/d
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	ca. 175 mg/kg bw
NOAEL teratogen.	:	ca. 450 mg/kg bw
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: purity: 99.4%
Result	:	450 mg/kg: significant maternal toxicity (reduced food intake, reduced maternal body weights and weight gain during dosing period; reduced gestational weight gain (day 0-21); clinical signs of toxicity: hypoactivity, ataxia, tremors, audible respiration, perioral wetness; increased relative liver weights) no embryotoxicity or teratogenicity was observed at any dosage level
Reliability	:	(1) valid without restriction

(23)

Species	:	Rabbit
Sex	:	Female
Strain	:	New Zealand white
Route of admin.	:	Gavage
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.	:	once daily
Duration of test	:	until day 29 of gestation
Doses	:	0, 50, 150, 300 or 500 mg/kg bw/d
Control group	:	Yes
Remark	:	8 rabbits/dose range-finding study
Result	:	50 mg/kg: one doe aborted; ataxia, twitching, gasping, audible, labored and rapid respiration; increased relative liver weights 150 mg/kg: maternal mortality 2/8; reduced food consumption on gd 7-9; significantly depressed body weight gain for gd 6-12; cleft palace in 1 fetus >= 300 mg/kg: reduced food consumption on gd 6-10; significantly elevated clinicals signs of toxicity (CNS and cardiopulmonary categories; see at 50 mg/kg) 300 mg/kg: maternal mortality 1/8; one doe aborted; reduced body weight on gd 12 and significantly depressed body weight gain on gd 6-12; increased preimplantation loss and increase in dead fetuses/litter; forelimb and pectoral girdle anomalies in 4 fetuses in 2 litters; cleft palate in 1 fetus; small tongue 500 mg/kg: maternal mortality 8/8

(24)

Species	:	Rabbit
Sex	:	Female
Strain	:	New Zealand white
Route of admin.	:	Gavage
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.	:	once daily
Duration of test	:	until day 29 of gestation
Doses	:	0, 5, 50 or 100 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	ca. 5 mg/kg bw
NOAEL teratogen.	:	ca. 100 mg/kg bw
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: purity: 99.7%
Result	:	>= 50 mg/kg: audible respiration and ocular discharge No embryotoxicity or teratogenicity was observed at any dosage employed.
Reliability	:	(1) valid without restriction

(25)

Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 7 through day 17 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	until post partum
Doses	:	90 mg/kg bw/d (30 ml/kg bw 0.3%)
Control group	:	Yes
Result	:	m-cresol was used as the solvent at a concentration of 0.3%; no negative effects on F0- or F1-generation were observed when compared with control animals.

(26)

Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 17 of gestation until 21 days after birth
Frequency of treatm.	:	Daily
Duration of test	:	until 8 w post partum
Doses	:	90 mg/kg bw/d (30 mg/kg 0.3%)
Control group	:	Yes
Result	:	m-cresol was used as the solvent at a concentration of 0.3%; no negative effects on F0-, F1- or F2-generation were observed when compared with controls (no fetotoxicity, normal postnatal development, normal behaviour and fertility).

(27)

Species	:	Mouse
Sex	:	Female
Strain	:	other: ICR-SLC
Route of admin.	:	s.c.
Exposure period	:	day 6 through day 15 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	until 5 w post partum
Doses	:	no data
Control group	:	Yes

Result : m-cresol was used as the solvent; no signs of fetotoxicity or teratogenicity, no maternal toxicity.

(28)

Species	:	Rabbit
Sex	:	Female
Strain	:	no data
Route of admin.	:	s.c.
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	until >= 12 d after exposure
Doses	:	30 mg/kg bw/d (10 ml/kg 0.3%)
Control group	:	Yes

Result : m-cresol was used as the solvent at a concentration of 0.3%; decreased maternal food consumption and body weight gain after day 14 of gestation, increased average number of implantations and reduced mean body weights in male fetuses, no increase of anomalies.

(29)

REFERENCES

(1) BioFax Ind., Bio-Test Lab, Inc., data Sheet 3-5/69

(2) NTP, NTP TOX 9, Toxicity studies of cresols in F344/N rats and B6C3F1mice, National Toxicology Program, Research Triangle Park, USA (1991)

(3) Dietz, D. & Mulligan, L.T., Subchronic toxicity of meta-cresol in Sprague Dawley rats, NTIS report no. PB88-195284. Microbiol. Assoc. Inc., Bethesda, USA (1988)

(4) Toxicity Research Lab.(TRL), Ltd., Subchronic neurotoxicity study in rats of ortho-, meta-, and para-cresol (TRL study #032-009). Michigan, 1986 (unpublished data submitted to the US-EPA), cited in EHC 168: Cresols, WHO, Geneva, 1995

(5) Shelley, W.B., Brit. J. Dermatol. 90, 169-174 (1974)

(6) Jansson, T. et al., Mutat. Res. 169, 129-139 (1986)

(7) Nestmann, E.R. et al., Mutat. Res. 79, 203-212 (1980)

(8) Florin, I. et al., Toxicology 18, 219-232 (1980)

(9) Hazleton Lab. Am., HLA Study No.10002-0-447, Mutagenicity test on meta-cresol in the rat primary hepatocyte unscheduled DNA synthesis assay, Kensington, USA (1988)

(10) Cheng, M. & Kligerman, A.D., Mutat. Res. 137, 51-55 (1984)

(11) Pool, B.L. et al., Mutat. Res. 213, 61-72 (1989)

(12) Moore, S.P. & Coohill, T.P., Prog. Nucl. Acids Res. Mol. Biol. 29, 149-153 (1983)

(13) Hejtmankova, N. et al., Acta Univ. Olumucensis, Fac. med. 74, 75-87 (1979)

(14) Ohshima, H. et al., Fd. Chem. Toxicol. 27, 193-203 (1989)

(15) Elespuru, R.K. & Pennington, R.W., Environ. Mutag. 3, 387 (1981)

(16) Levan, A. & Tjio, J.H., Hereditas 34, 453-484 (1948)

(17) Hazleton Lab. Am., HLA Study No. 10002-0-431, Mutagenicity test on meta-cresol in a mouse lymphoma mutation assay, Kensington, USA, 1988, at the request of CMA, USA

(18) Sharma, A.K. & Ghosh, S., The Nucleus 8, 183-190 (1965)

(19) Pool, B.L. & Lin, P.Z., Fd. Chem. Toxic. 20, 383-391 (1982)

(20) Haworth, S. et al., Environ. Mutagen., Suppl. 1, 3-142 (1983)

(21) Hazleton Lab. Am., HLA Study No. 10002-0-437, Mutagenicity test on m-cresol in and in-vitro cytogenetic assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary (CHO) cells, Kensington, USA, 1988, at the request of CMA, USA

(22) Hazleton Lab. Am., HLA Study No. 10002-0-451, Mutagenicity test on meta-cresol in a mouse bone marrow cytogenetic assay, Kensington, USA, 1988, at the request of CMA, USA

(23) Bushy Run Research Center, Project report 51-509, Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to Sprague-Dawley (CD) rats, June (1988), at the request of CMA, USA

(24) Bushy Run Research Center, (BRRC Project No. 87-81-96103), Developmental toxicity dose-range finding study of o-, m-, or p-cresol administered by gavage to New Zealand White rabbits, 1987, at the request of CMA, USA

(25) Bushy Run Research Center,Project Report 51-508, Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to New Zealand White rabbits, June (1988), at the request of CMA, USA

(26) Akatsuka, K. et al., Oyo Yakuri 16, 1169-1179 (1978)

(27) Akatsuka, K. et al., Oyo Yakuri 16, 1181-1190 (1978)

(28) Akatsuka, K. et al., Oyo Yakuri 14, 369-378 (1977)

(29) Akatsuka, K. et al., Oyo Yakuri 16, 1191-1199 (1978)

APPENDIX E
ROBUST SUMMARY FOR p-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	83 - 87 mg/kg bw
LOAEL	:	242 - 256 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%

Remark :

Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25
1000 ppm	87	83
3000 ppm	256	242
10000 ppm	835	769
30000 ppm	2180	2060

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result :

There were no deaths. Decreased mean final body weights, body weight gains and feed consumption occurred in both the top-dose males and females. These animals also showed clinical signs of toxicity, including hunched posture and rough hair coat.
Increased relative liver and kidney weights were recorded in females fed >/= 242 mg/kg bw/day or 2060 mg/kg bw/day, respectively and in males fed >/= 835 mg/kg bw/day. No gross lesions were noted at necropsy.

gross lesions were noted at necropsy.
Histopathological evaluation revealed effects in the uterus in the top-dose females; in the nasal cavity in both males and females at >/= 256 and >/= 242 mg/kg bw/day, respectively; and bone marrow in both males and females at >/= 256 and >/= 769 mg/kg bw/day, respectively.

Reliability : (1) valid without restriction

(1)

Type : Repeat dose
Species : Mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : ad libitum
Post exposure period : None
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm
Control group : yes, concurrent no treatment
NOAEL : 50 - 60 mg/kg bw
LOAEL : 60 - 163 mg/kg bw
Method : EPA OTS 795.2600
Year : 1992
GLP : Yes
Test substance : other TS: purity > 98%

Remark : Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	50	60
1000 ppm	163	207
3000 ppm	469	564
10000 ppm	1410	1590

Consumption data for the top dose were not calculated due to 100% mortality at this level.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : There was 100% mortality at the highest dose level. One male receiving 1410 mg/kg bw/day also died. Mean final body weights and mean body weight gains for surviving males at 1410 mg/kg bw/day were significantly lower than in the control groups; feed consumption was depressed at the beginning of the study in males at 1410 mg/kg bw/day and in females at 1590 mg/kg bw/day. Clinical signs of toxicity included hunched posture, rough hair coat, lethargy, and hypothermia in the top-dose females

hair coat, lethargy, and hypothermia in the top-dose females that died and, together with laboured breathing and paleness, in the males fed >/= 1410 mg/kg bw/day.
Relative liver weight was increased in females receiving >/= 564 mg/kg bw/day; in males, the relative liver and heart weights were increased at 1410 mg/kg bw/day and relative kidney weight at >/= 469 mg/kg bw/day. No gross lesions were noted at necropsy.
Histopathological evaluation revealed nasal lesions in the females at all doses and in males at >/= 163 mg/kg bw/day. In the top-dose animals which died, renal and hepatic necrosis and bone marrow hypocellularity was noted.

Reliability : (1) valid without restriction

(1)

Type : Repeat dose
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : 13 weeks
Frequency of treatm. : 7 days/week

Doses : 0, 50, 175, 600 mg/kg bw/day
Control group : Yes
LOAEL : 50 mg/kg bw
Method : other
Year :
GLP : no data
Test substance : no data

Remark : Groups of 30 rats/sex were administered p-cresol in corn oil. The original data are unpublished and are available from the US EPA Freedom of Information Office. No further experimental details are available from the citing reviews (ATSDR, 1990; IPCS, 1993).

Result : 600 mg/kg: There was some mortality. Overt signs of toxicity at this dose included lethargy, tremors, convulsions and coma. There was also a decrease in the body weight gains. In females, increased serum enzyme levels were observed, which were correlated with the presence of hepatic inflammation, and serum cholesterol. The relative heart and liver weights of males were increased and their absolute brain weight decreased. Females showed decreased absolute brain and ovary weights. Microscopic examination revealed a small increased incidence of epithelial metaplasia of the trachea in both sexes.
>/= 175 mg/kg: serum protein levels and relative kidney weight were increased in the males and blood effects (decreased red blood cell count and haemoglobin and haematocrit values) observed in the females.
A small increase in the incidence of nephropathy, which did not appear to be dose-related, was seen in the males at all dose levels.

Reliability : (2) valid with restrictions

(2)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, 100, 1535, 1537.
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975; to select dose range the chemical was checked for toxicity to S. typh. TA100
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

(3)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	30 to 902 ug/ml
Metabolic activation	:	with and without
Result	:	Positive
Method	:	other: similar to OECD Guideline 473
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Method	:	Duplicate CHO cultures were incubated with 15-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 30-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay.
Result	:	Increases in chromosomally aberrant cells were observed in the nonactivation assay at all doses. Increases in the chromosomally aberrant cells were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/ml.
Reliability	:	(1) valid without restriction

(4)

Type	:	other: cell transformation assay
System of testing	:	mouse BALB/c-3T3 cells
Test concentration	:	0.81 nl/ml, 3.25 nl/ml, 5 nl/ml, 10 nl/ml, and 15 nl/ml
Cycotoxic concentr.	:	31.3 nl/ml
Metabolic activation	:	Without
Result	:	Positive
Method	:	EPA OTS 795.2850
Year	:	1988

GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(5)

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y mouse lymphoma cells
Test concentration	:	with activation: 0.256 ug/ml, 0.511 ug/ml, 0.767 ug/ml, 1.02 ug/ml, 1.53 ug/ml, and 3.07 ug/ml. without activation: 51.1 ug/ml, 102 ug/ml, 153 ug/ml, 204 ug/ml, 307 ug/l, and 409 ug/ml.
Cycotoxic concentr.	:	with activation: 5.11 ug/ml. without activation: 511 ug/ml.
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: similar to OECD Guideline 476
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(6)

Type	:	DNA damage and repair assay
System of testing	:	human lymphocytes
Test concentration	:	5 x 10-6 - 25 x 10-6 M
Metabolic activation	:	Without
Result	:	Positive
Method	:	Other
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Method	:	p-Cresol was tested for its ability to inhibit semiconservative DNA synthesis. Initially, DNA repair was induced by irradiation and, in these cells, semiconservative DNA synthesis was blocked by treatment with with hydroxyurea. In both studies, cells were treated with radiolabelled thymidine for 2 hours and incorporation of thymidine into the cells was measured.
Result	:	p-Cresol inhibited both UV-induced DNA repair synthesis and semiconservative DNA synthesis as seen by a reduction in radiolabelled thymidine incorporation. It was unclear from the report if this inhibition was seen at all concentrations tested but at the top dose, 21% inhibition of DNA repair synthesis and 25% inhibition of semiconservative DNA synthesis was found.

(7)

Type	:	Sister chromatid exchange assay
System of testing	:	human lymohocytes
Test concentration	:	0 - 0.5 Mm
Metabolic activation	:	no data

Result	:	Negative
Method	:	Other
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, 99.9% purity
Remark	:	Styrene-7,8-oxide acted as the positive control. Cells were incubated with p-cresol for 88-90 hr before being analysed. This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

(8) (9)

Type	:	Ames test
System of testing	:	Salmonella typhimurium strains TA98, 100, 1535, 1537, TA1538
Test concentration	:	0, 0.5, 5, 50, 500, 5000 ug/plate dissolved in DMSO, highest dose cytotoxic
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1975
GLP	:	no data
Test substance	:	other TS: purity : 98%
Reliability	:	(1) valid without restriction

(10)

GENETIC TOXICITY 'IN VIVO'

Type	:	Dominant lethal assay
Species	:	Mouse
Sex	:	male/female
Strain	:	ICR
Route of admin.	:	Gavage
Exposure period	:	Single dose
Doses	:	0, 100, 275, and 550 mg/kg
Result	:	Negative
Method	:	EPA OTS 798.5450
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(11)

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	Male
Strain	:	other: Oregon-R
Route of admin.	:	oral feed
Exposure period	:	3 days

Doses	:	0, 60, 300 and 600 ug/ml 5% sucrose
Result	:	Negative
Method	:	EPA OTS 798.5275
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 99.8% purity
Reliability	:	(1) valid without restriction

(12)

Type	:	Sister chromatid exchange assay
Species	:	Mouse
Sex	:	Male
Strain	:	DBA
Route of admin.	:	i.p.
Exposure period	:	single dose
Doses	:	0, 75 mg/kg bw in sunflower oil
Result	:	Negative
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	other TS: p-cresol, purity >99%; obtained from Aldrich Chemical Co.
Method	:	p-Cresol was administered to 2 or 3 intact or hepatectomized male mice by single intraperitoneal injection. Negative and positive controls received 0.35 ml sunflower oil (4 intact and 5 hepatectomized animals) and 5 mg cyclophosphamide/kg bw (2 intact animals), respectively. After 30 min, DNA labelling was initiated using BrdU. After a further 21 hr the animals were killed, cells isolated and harvested and sister chromatid exchange (SCE) frequency in bone marrow cells, alveolar macrophages and regenerating liver cells analysed. Some of the mice were partially hepatectomized to induce liver cell regeneration.
Result	:	p-Cresol did not induce significant increases in SCE frequencies in any of the cell types examined. The doses tested were overtly toxic to the mice, causing lethargy, piloerection and lacrimation.
Reliability	:	(2) valid with restrictions

(13)

TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	see remarks
Frequency of treatm.	:	5 days per week
Premating exposure period		

Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	see remarks
No. of generation studies	:	2
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 rats/sex/group
Control group	:	yes, concurrent vehicle
NOAEL parental	:	ca. 30 mg/kg bw
NOAEL F1 offspring	:	ca. 175 mg/kg bw
NOAEL F2 offspring	:	ca. 175 mg/kg bw
other: NOAEL (fertility)	:	ca. 450 mg/kg bw
Method	:	EPA OPP 83-4
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 98.93% pure
Remark	:	Groups of rats were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.
Result	:	Clinical signs of toxicity occurred in F0 and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in F0 males), and perioral wetness occurred at >= 175 mg/kg bw. No reproductive parameters were effected in either of the two generations (F1 or F2). p-Cresol caused increased still births in the F1 and F2 generations: in F1 pups at 175 (but not 450) mg/kg/day and in F2 pups at 30 and 450 (but not 175) mg/kg/day. There was some variability in the number of stillborn in control groups in F1 and F2 generation (2 versus 0) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups: 0/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not affected by treatment.
Reliability	:	(1) valid without restriction

(14)

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	days 6 – 15

Frequency of treatm.	:	Daily
Duration of test	:	10 days
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 175 mg/kg bw
NOAEL teratogen.	:	= 175 mg/kg bw
Method	:	EPA OPP 83-3
Year	:	1988
GLP	:	Yes
Test substance	:	Other TS: p-cresol. purity = 98.93%
Remark	:	p-Cresol was administered in corn oil.
Result	:	Maternal toxicity occurred at 450 mg/kg bw/day and included death, decreased food consumption and body weight gain, audible respiration, hypoactivity, ataxia and tremors. p-Cresol caused mild fetotoxicity at the 450 mg/kg, as seen by reduced ossification in three skeletal districts. In addition, fetal body weight was reduced at the 450 mg/kg dose level. There was no treatment-related increased incidence of malformations at any dosage.
Reliability	:	(1) valid without restriction

(15)

Species	:	Rabbit
Sex	:	Female
Strain	:	New Zealand white
Route of admin.	:	Gavage
Exposure period	:	Days 6 - 18 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	24 days
Doses	:	0, 5, 50, 100 mg/kg bw/day; 14 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	< 50 mg/kg bw
NOAEL teratogen.	:	= 100 mg/kg bw
Method	:	EPA OPP 83-3
Year	:	1988
GLP	:	Yes
Test substance	:	Other TS: p-cresol. purity = 98.93%
Remark	:	p-Cresol was administered in corn oil.
Result	:	Maternal toxicity including audible respiration, ocular discharge, hypoactivity and death were seen at 50 mg/kg bw/day or above. p-Cresol had no effects on the developing embryos at any of the doses tested.
Reliability	:	(1) valid without restriction

(15)

Species	:	Rat
Sex	:	Male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	10 weeks prior to mating through life
Frequency of treatm.	:	Daily
Duration of test	:	Lifelong
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 animals/sex/group

Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 175 mg/kg bw
NOAEL teratogen.	:	= 175 mg/kg bw
Method	:	Other: EPA OPP 83-4
Year	:	1989
GLP	:	Yes
Test substance	:	Other TS: p-cresol, purity >98%
Remark	:	Developmental endpoints were also monitored in the 2-generation reproduction studies in rats discussed previously. Groups of rats were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.
Result	:	p-Cresols caused effects on pup bodyweight at some time during development when given at 450 mg/kg bw/day; a dose causing overt parental toxicity. Occasional bodyweight changes were seen at lower doses but it is not clear if these were treatment-related.
Reliability	:	(1) valid without restriction

(14)

REFERENCES

(1) NTP. 1992. Toxicity studies of cresols (CAS Nos 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program.

(2) Microbiological Associates. 1988. Subchronic toxicity of para-cresol in Sprague-Dawley rats. Unpublished data submitted by Microbiological Associates to US EPA.

(3) Haworth S. et al., Salmonella mutagenicity test results for 250 chemicals, Environ. Mutagen. Suppl. 1: 3-142, 1983

(4) Hazleton Laboratories America, Inc. HLC study no: 10003-0-437. Mutagenicity Test on para-Cresol CP 945 In an In Vitro Cytogenetic Assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary (CHO) Cells. June 28, 1988. Unpublished data submitted to EPA/OTS.

(5) Hazleton Laboratories America, Inc. HLA Study No.: 10003-0-441. Genetic Toxicology Test on Para-Cresol in the In Vitro Transformation of BALB/C-3T3 Cells Assay. June 27, 1988. Unpublished data submitted to EPA/OTS 0517691.

(6) Hazleton Labs. Mutagenicity tests of p-cresol and m-cresol in a mouse lymphoma mutation assay. Unpublished data submitted to EPA/OTS (Fiche No. OTS0517693), 1988.

(7) Daugherty J.P. & Franks H. 1986. Effect of monocyclic derivatives on DNA repair in human lymphocytes. Res. Commun. Chem. Path. Pharmac. 54: 133-136.

(8) Additional reference:
Cheng M. & Kligerman A.D. Evaluation of the genotoxicity of cresols using sister-chromatid exchange (SCE). Mutation Res. 137: 51-55, 1984.

(9) Jansson T. et al. In vitro studies of biological effects of cigarette smoke condensate II. Induction of sister-chromatid exchanges in human lymphocytes by weakly acidic, semivolatile constituents. Mutation Res. 169: 129-139, 1986.

(10) Pool B.L. et al., FD, Chem. Toxic 20, 383-391 (1982).

(11) Hazelton Laboratories America Inc., James L. Ivett., Dominant Lethal Assay in Mice; para-cresol., June 30, 1989.

(12) Hazleton Labortories America, Inc., Russell C. Seranau., Mutagenicity test on para-cresol Drosophila Melanogaster sex-linked recessive lethal test., February 22, 1989.

(13) Cheng M. & Kligerman A.D. Evaluation of the genotoxicity of cresols using sister-chromatid exchange (SCE). Mutation Res. 137: 51-55, 1984.

(14) BRRC. 1989. Teresa L. Neeper-Bradley and Rochelle W. Tyl., Two-generation reproduction study of p-cresol (CAS No. 106-44-5) administered by gavage to Sprague-Dawley (CD) rats. Project report 52-512. November 13, 1989. Unpublished data submitted by Bushy Run Research Center to The American Chemistry Council Cresols Panel, Washington, DC.

(15) BRRC. 1988. Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to Sprague-Dawley (CD) rats. Unpublished data submitted by Bushy Run Research Center to EPA/OTS (Fiche No. OTS0517695).

APPENDIX F
ROBUST SUMMARY FOR o-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	Male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	83-87 mg/kg bw
LOAEL	:	242-256 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in high-dose females; body weight gains and feed consumption occurred in both the top-dose males and females. Increased liver and kidney weights were recorded in the top two dose groups. Relative liver and kidney weights were increased in the top three and top two dose groups for males and females, respectively. No gross or histopathologic lesions were noted at necropsy.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1

Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	50-60 mg/kg bw
LOAEL	:	60-163 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	Mean final body weights and mean body weight gains reduced for males at top two dose groups; feed consumption was depressed at the beginning of the study in males top two dose levels. Clinical signs of toxicity, including hunched posture, rough hair coat and lethargy, were noted in high-dose animals. Hypothermia, rapid breathing and tremors were noted in the top-dose males. Relative liver weight was increased in the three highest dose groups. Relative kidney weights were increased in high-dose females. No gross lesions were noted at necropsy. Histopathological evaluation revealed ovarian atrophy in the high dose and uterine atrophy in the top dose levels.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	7 days/week
Doses	:	0, 50, 175, 600 mg/kg bw/day
Control group	:	Yes
LOAEL	:	50 mg/kg bw
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data

Remark	:	Groups of 30 rats/sex were administered p-cresol in corn oil. The original data are unpublished and are available from the US EPA Freedom of Information Office. No further experimental details are available from the citing reviews (ATSDR, 1990; IPCS, 1993).
Result	:	600 mg/kg: Mortality in 19/30 females and 9/30 males. Overt signs of toxicity at this dose included CNS depresion, lethargy, tremors, and convulsions occurring within one hour post-dosing but not beyond one hour post-dosing. High-dose male body weight gain suppression. No effects on clinical chemistry, hematology, urinalysis, no treatment-related ophthalmic lesions, no effect on organ weights, no treatment-related gross or microscopic lesions.
Reliability	:	(2) valid with restrictions

(2)

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 1880, 3750, 7500, 15000 9r 30000 ppm
Control group	:	yes, concurrent no treatment
LOAEL	:	7500 ppm (relative and absolute liver weight)
NOAEL	:	15000 ppm
Year	:	1992
GLP	:	No
Test substance	:	other TS: purity > 98%
Remark	:	Groups of 20 rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in high-dose males; body weight gains and feed consumption occurred in both males and females of the top two doses. Increased liver and kidney weights were recorded in the top two dose groups (three dose groups for liver weight). Relative testes weight was increased in high-dose males and relative thymus weight was increased in males of the top two dose groups. There was evidence of increased bone marrow hypocellularity in males of the top dose and females of the top two doses.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 1250, 2500, 5000, 10000 or 20000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	2500 ppm (female body weight)
LOAEL	:	5000 ppm
	:	
Year	:	1992
GLP	:	No
Test substance	:	other TS: purity > 98%

Remark : Groups of 10 mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : Mean final body weights and mean body weight gains reduced for males at the top dose and females of the top three dose groups; feed consumption was depressed at the beginning of the study in the high-dose groups. Clinical signs of toxicity included hunched posture, rough hair coat were noted in high-dose male animals. All male dose groups and females of the three highest dose groups had relative liver weight increases. Relative kidney weights were increased in high-dose females. High-dose males had increased relative testes weight. Relative thymus weight was increased in high-dose animals. Histopathological evaluation revealed minimal forestomach atrophy in the high dose groups.

Reliability : (1) valid without restriction

(1)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, 100, 1535, 1537.
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975); to select dose range the chemical was checked for toxicity to S. typh. TA100
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

(3)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	30 to 902 ug/ml
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	Positive
Method	:	other: similar to OECD Guideline 473
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Method	:	Duplicate CHO cultures were incubated with 15-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 30-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay.
Result	:	Increases in chromosomally aberrant cells were observed in the nonactivation assay at all doses. Increases in the chromosomally aberrant cells were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/ml.
Reliability	:	(1) valid without restriction

(4)

Type	:	other: cell transformation assay
System of testing	:	mouse BALB/c-3T3 cells
Test concentration	:	0.81 nl/ml, 3.25 nl/ml, 5 nl/ml, 10 nl/ml, and 15 nl/ml
Cycotoxic concentr.	:	31.3 nl/ml
Metabolic activation	:	Without
Result	:	Positive
Method	:	EPA OTS 795.2850
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: 99.8% pure

Reliability : (1) valid without restriction

(5)

Type : Mouse lymphoma assay
System of testing : L5178Y mouse lymphoma cells

Metabolic activation : with and without
Result : Negative
Method : other: similar to OECD Guide-line 476
Year : 1988
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(6)

Type : DNA damage and repair assay
System of testing : E. coli

Metabolic activation : With and without
Result : Negative
Method : Other
Year : 1980
GLP : no data
Test substance : other TS: o-cresol, purity not noted
Flag : Critical study for SIDS endpoint

(7)

Type : Sister chromatid exchange assay
System of testing : human lymohocytes
Test concentration : 0 - 0.5 Mm

Metabolic activation : no data
Result : Negative, Equivocal
Method : Other
Year : 1986
GLP : no data
Test substance : other TS: o-cresol, 99.9% purity

Remark : Styrene-7,8-oxide acted as the positive control. Cells were incubated with p-cresol for 88-90 hr before being analysed.
This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

(8) (9)

Type : Unscheduled DNA Synthesis
System of testing : Rat hepatocytesi

Result : Negative

Method : Other
Year : 1981
GLP : no data
Test substance : other TS: o-cresol, purity not noted

(10)

Type : *In Vitro* Cell Transformation
System of testing : BALB 3T3

Result : **Negative**

Year : **1981**
GLP : **No data**
Test substance : **o-cresol**

(11)

GENETIC TOXICITY 'IN VIVO'

Type : Dominant lethal assay
Species : Mouse
Sex : male/female
Strain : ICR
Route of admin. : Gavage
Exposure period : Single dose
Doses : 0, 75, 250, and 750 mg/kg
Result : Negative
Method : EPA OTS 798.5450
Year : 1989
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(12)

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : Male
Strain : other: Oregon-R
Route of admin. : oral feed
Exposure period : 3 days
Doses : 0, 100, 500 and 1000 ug/ml 5% sucrose
Result : Negative
Method : EPA OTS 798.5275
Year : 1989
GLP : Yes
Test substance : Other TS: 99.8% purity

Reliability : (1) valid without restriction

(13)

TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	see remarks
Frequency of treatm.	:	5 days per week
Premating exposure period		
Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	see remarks
No. of generation studies	:	
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 rats/sex/group
Control group	:	yes, concurrent vehicle
NOAEL parental	:	ca. 30 mg/kg bw
NOAEL F1 offspring	:	ca. 175 mg/kg bw
NOAEL F2 offspring	:	ca. 175 mg/kg bw
other: NOAEL (fertility)	:	ca. 450 mg/kg bw
Method	:	EPA OPP 83-4
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 98.93% pure

Remark : Groups of rats were administered o-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.

Result : Clinical signs of toxicity occurred in F0 and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in F0 males), and perioral wetness occurred at >= 175 mg/kg bw.

No reproductive parameters were effected in either of the two generations (F1 or F2).
o-Cresol caused increased still births in the F1 and F2 generations: in F1 pups at 175 (but not 450) mg/kg/day and in F2 pups at 30 and 450 (but not 175) mg/kg/day. There was some variability in the number of stillborn in control groups in F1 and F2 generation (2 versus 0) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups: 0/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not affected by treatment.

affected by treatment.

Reliability : (1) valid without restriction

(14)

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	days 6-15
Frequency of treatm.	:	Daily
Duration of test	:	10 days
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 175 mg/kg bw
NOAEL teratogen.	:	= 175 mg/kg bw
Method	:	EPA OPP 83-3
Year	:	1988
GLP	:	Yes
Test substance	:	Other TS: o-cresol, purity = 98.93%
Remark	:	o-Cresol was administered in corn oil.
Result	:	Maternal toxicity occurred at 450 mg/kg bw/day and included death, decreased food consumption and body weight gain, audible respiration, hypoactivity, ataxia and tremors. There was no treatment-related increased incidence of malformations at any dosage.
Reliability	:	(1) valid without restriction

(15)

Species	:	Rabbit
Sex	:	Female
Strain	:	New Zealand white
Route of admin.	:	Gavage
Exposure period	:	Days 6-18 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	24 days
Doses	:	0, 5, 50, 100 mg/kg bw/day; 14 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	5 mg/kg bw
NOAEL developmental	:	50 mg/kg bw
Method	:	EPA OPP 83-3
Year	:	1988
GLP	:	Yes
Test substance	:	Other TS: o-cresol, purity = 98.93%
Remark	:	o-Cresol was administered in corn oil.
Result	:	Maternal toxicity including audible respiration, ocular discharge were seen at 50 mg/kg bw/day or above. o-Cresol had no effects on the developing embryos at any of the doses tested.
Reliability	:	(1) valid without restriction

REFERENCES

(1) NTP. 1992. Toxicity studies of cresols (CAS Nos 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program.

(2) Microbiological Associates. 1988. Subchronic toxicity of ortho-cresol in Sprague-Dawley rats. Unpublished data submitted by Microbiological Associates to US EPA.

(3) Haworth S. et al., Salmonella mutagenicity test results for 250 chemicals, Environ. Mutagen. Suppl. 1: 3-142, 1983

(4) Hazleton Laboratories America, Inc. HLC study no: 10003-0-437. Mutagenicity Test on ortho-Cresol In an In Vitro Cytogenetic Assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary (CHO) Cells. June 28, 1988. Unpublished data submitted to EPA/OTS.

(5) Hazleton Laboratories America, Inc. HLA Study No.: 10003-0-441. Genetic Toxicology Test on ortho-Cresol in the In Vitro Transformation of BALB/C-3T3 Cells Assay. June 27, 1988. Unpublished data submitted to EPA/OTS 0517691.

(6) Hazleton Labs. Mutagenicity tests of o-cresol in a mouse lymphoma mutation assay. Unpublished data submitted to EPA/OTS (Fiche No. OTS0517693), 1988.

(7) Daugherty J.P. & Franks H. 1986. Effect of monocyclic derivatives on DNA repair in human lymphocytes. Res. Commun. Chem. Path. Pharmac. 54: 133-136.

(8) Cheng M. & Kligerman A.D. Evaluation of the genotoxicity of cresols using sister-chromatid exchange (SCE). Mutation Res. 137: 51-55, 1984.

(9) Jansson T. et al. In vitro studies of biological effects of cigarette smoke condensate II. Induction of sister-chromatid exchanges in human lymphocytes by weakly acidic, semivolatile constituents. Mutation Res. 169: 129-139, 1986.

(10) MRI Project No. 4822-2, March, 1980. Unpublished report.

(11) LBI Project No. 20991, July, 1981, Unpublished report.

(12) Hazelton Laboratories America Inc., James L. Ivett., Dominant Lethal Assay in Mice; para-cresol., June 30, 1989.

(13) Hazleton Labortories America, Inc., Russell C. Seranau., Mutagenicity test on ortho-cresol Drosophila Melanogaster sex-linked recessive lethal test, February 22, 1989.

(14) BRRC. 1989. Teresa L. Neeper-Bradley and Rochelle W. Tyl., Two-generation reproduction study of o-cresol (CAS No. 95-48-7) administered by gavage to Sprague-Dawley (CD) rats. December 19, 1989. Unpublished data submitted by Bushy Run Research Center to The American Chemistry Council Cresols Panel, Washington, DC.

(15) BRRC. 1988. Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to Sprague-Dawley (CD) rats. Unpublished data submitted by Bushy Run Research Center to EPA/OTS (Fiche No. OTS0517695).

(16) BRRC. 1988. Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to New Zealand White Rabbits. Unpublished data submitted by Bushy Run Research Center to EPA/OTS (Fiche No. OTS0517695).

APPENDIX G
ROBUST SUMMARY FOR MIXED CRESOL ISOMERS TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	Male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	300 ppm
LOAEL	:	1000 ppm nasal respiratory hyperplasia in females
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in high-dose males; body weight gains and feed consumption occurred in both the top-dose males and females. Increased relative kidney weights were recorded in the top two dose groups of each sex. Relative liver weights were increased in the top three and top four dose groups for males and females, respectively. High-dose males had an increased relative testes weight. No gross lesions were noted at necropsy. Hyperplasia of the respiratory , epithelium of the nasal cavity was observed in the top three dose levels, both sexes. Mild-to-moderate bone marrow hypoplasia was seen in the top three male dose groups and the top two female dose groups. Minimal-to-mild esophagus and forestomach hyperplasia was reported for males and females of the top three dose groups.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	50-60 mg/kg bw
LOAEL	:	60-163 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no unschedule deaths in the study. Mean final body weights and mean body weight gains were reduced for high-dose males and females. Body weight gain was suppressed in the top three dose groups of males. Feed consumption was depressed at the beginning of the study. Clinical signs of toxicity in high-dose animals were: alopecia, dehydration, hunched posture, rough hair coat, hypothgermia and lethargy. Relative liver weight was increased in the four highest dose groups of males and the three highest dose groups of females. High-dose males had a relative increase in testes weight. High-dose fermales had increased relative kidney weights. No gross lesions were noted at necropsy. Histopathological evaluation revealed epithelial hyperplasia of varying degrees throughout the respiratory tract.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum

Post exposure period	:	None
Doses	:	0, 1880, 3750, 7500, 15000 or 30000 ppm
Control group	:	yes, concurrent no treatment
LOAEL	:	7500 ppm (relative and absolute liver weight)
NOAEL	:	15000 ppm
Year	:	1992
GLP	:	No
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of 20 rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in the two highest-dose males and female groups; feed consumption suppressed in high-dose groups of both sexes in first week of study. Increased relative kidney weights were recorded in the top three male dose groups and the top female dose group. Relative liver weight was elevated for animals of the top three dose groups. Relative testes weight was increased in the top two male dose groups. There was dose-related evidence of hyperplasia of the nasal respiratory epithelium. Thyroid follicle changes (increased colloid formation) was reported for males and females in a dose-related manner. Minimal increased bone marrow hypocellularity was reported for males of the top dose and females of the top dose group. Minimal-to-mild uterine atrophy was reported for the two top dose groups.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 625, 1250, 2500, 5000, 10000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	2500 ppm (female body weight)
LOAEL	:	5000 ppm
Year	:	1992
GLP	:	No

Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of 10 mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no unscheduled deaths during the study. Mean final body weights and mean body weight gain (males) were reduced for high-dose animals; feed consumption was slightly depressed in the high-dose groups. Male dose groups (top two dose groups) and females of the highest dose groups had relative liver weight increases. There were no liver lesions reported from microscopic examination. Histopathological evaluation revealed hyperplasia of the nasal respiratory epithelium.
Reliability	:	(1) valid without restriction

(1)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 97, TA 98, 100, 1535.
Test concentration	:	0.0, 10.0, 33.0, 100.0, 333.0, 1000 and 3333 or 6666 ug/plate
Metabolic activation	:	with and without hamster and rat S-9
Result	:	Negative
Method	:	Method of Zeiger, et al., 1988.
Year	:	1990
GLP	:	no data
Test substance	:	m-/p-cresol 60%/40% mixture; other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y mouse lymphoma cells
Metabolic activation	:	with and without
Result	:	Positive with, weakly positive without
Method	:	other: similar to OECD Guideline 476
Year	:	1980
GLP	:	Yes

Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

Reliability : (1) valid without restriction

(2)

Type : Sister chromatid exchange assay
System of testing : Chinese hamster ovary cells

Metabolic activation : With and without
Result : Positive with and without
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(2)

Type : Cell transformation
System of testing : Mouse BALB/C 3T3 cells

Metabolic activation : With
Result : Positive
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(2)

Type : Unscheduled DNA Synthesis
System of testing : Rat hepatocytes

Result : Positive
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(3)

GENETIC TOXICITY "IN VIVO"

Type : Micronuclei in peripheral blood erythrocytes
Species : Mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : Oral feed
Exposure period : Daily for 13 weeks
Doses : 0, 625, 1250, 2500, 5000, 10000 ppm
Result : Negative
Method : MacGregor et al, 1983; 10000 normochromic erythrocytes were scored for each animal
Year : 1990
GLP : Yes
Test substance : m/p-cresol, 60%-40% mix TS: purity > 98%

Reliability : (1) valid without restriction

(1)

REFERENCES

(1) NTP. 1992. Toxicity studies of cresols (CAS Nos 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program.

(2) Litton Bionetics Unpublished report. Sister Chromatid Exchange Assay, Ames Test, Mouse Lymphoma Forward Mutation Assay, and Transformation Assay for a Sample Containg 33-1/3% each ortho-, meta- and para-cresol. EPA/OTS Report OTSO517528.

(3) Litton Bionetics Unpublished report. Unscheduled DNA Synthesis Assay for a Sample Containg 33-1/3% each ortho-, meta- and para-cresol. EPA/OTS Report OTSO517530.